Communication

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Copper-catalyzed C-H Azidation of Anilines under Mild Conditions

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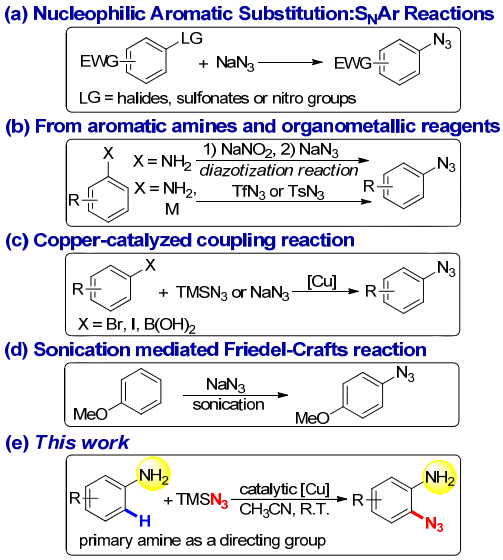
Supporting Information Placeholder

ABSTRACT: A novel and efficient copper catalyzed azidation reaction of anilines *via* C-H activation has been developed. This method involves primary amine as directing group, by coordinating with the metal center, *ortho* azidation products are regioselectively obtained under mild conditions. This effective route to synthesis aryl azide is of great significance in view of the versatile reactivity of the azide product.

The first organic azide, phenyl azide, was discovered by Peter Griess in 1864.[1] Since then, numerous syntheses of these energy-rich molecules have been developed. In most recent times, organic azides are widely used in organic synthesis as valuable intermediates and building blocks due to their versatile reactivities,[2] elegant perspectives have been developed for the application of organic azide, in particular in the synthesis of nitrogen-containing heterocycles, in peptide chemistry, material science, polymer chemistry and drug discovery.[3] Moreover, aryl azide has found its biological and industrial use as photoaffinity labeling agents.[4] Thus, organic azides have assumed an important position at the interface between chemistry, biology, medicine, and materials science.

Conventional methods incorporation of the azide group into aromatic rings[5] include 1) classical nucleophilic aromatic substitution (S_NAr) reaction while this requires activated aromatic systems bearing an electron-withdrawing group (a, Scheme 1);[6] 2) diazotization of aromatic amines in strong acidic condition and subsequent treatment with sodium azide, or diazo transfer reaction by treatment of aromatic amines with triflyl azide (b, Scheme 1);[7] 3) reactions of tosyl azide with organometallic reagents (b, Scheme 1).[8] 4) copper catalyzed coupling reaction of aryl halides or aryl boronic acids (c, Scheme 1).[9] More recently, a sonication-mediated C-H azidation of anisole has been reported through a Friedel-Crafts reaction process with the azide at *para* position (d, Scheme 1).[10] However, these methods suffer from narrow functional group compatibility, atom uneconomy and harsh conditions which may induce decomposition process of azides. Hence, developing new ways to obtain aryl azides involving direct C-H functionalization[11, 12] under mild conditions would be very fascinating while challenging at the same time.

Scheme 1. Azide group incorporation into aromatic rings.

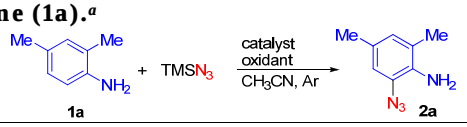


On the other hand, directed *ortho* functionalization of arenes through C-H activation have emerged as an effective tool to construct substituted arenes.[11,13,14] Although various nitrogen-containing groups have been employed as directing group, the *ortho* C-H functionalization of arenes directed by primary amine is still limited. The amine group of aniline substrates assisted vinyl C-H bond activation and alkenylation were individually disclosed by the groups of You[15] and Zhang.[16]

Herein, we report a novel and efficient Cu-catalyzed C-H azidation of aniline derivatives directed by amino group under mild conditions (e, Scheme 1). The signific-

ance of the present chemistry is threefold: 1) To the best of our knowledge, this is a novel amino group directed *ortho* C-H functionalization of simple and readily available anilines. Moreover, the amino group could be converted into Cl, Br, I, CN, OH and H by Sandmeyer reaction; 2) Although various C-C and C-Heteroatom bond formations *via* C-H activation have been successfully achieved, the directed *ortho* C-H azidation of arenes has not been realized till this work; 3) In contrast to employing expensive transition metal catalyst, this process is simple, proceeds under mild conditions, uses inexpensive copper catalysts, and forms valuable products that would be difficult to synthesize by other methods.

Table 1. Cu-catalyzed Azidation of 2, 4-Dimethyl aniline (1a).[a]



1a 2a

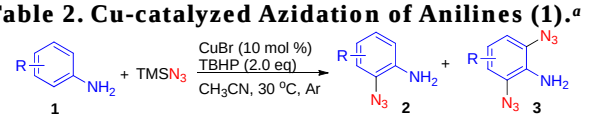
entry	catalyst (mol %)	oxidant (equiv)	T (°C)	time (h)	yield (%)[b]
1	CuBr (10)	TBHP (2.0)	60	12	28
2	CuBr (10)	TBHP (2.0)	30	12	27
3	CuBr (10)	TBHP (2.0)	30	1	56
4	**CuBr (10)**	**TBHP (2.0)**	**30**	**2**	**68**
5	CuBr (10)	TBHP (1.2)	30	2	54
6	CuBr (5)	TBHP (2.0)	30	2	40
7	CuCl (10)	TBHP (2.0)	30	2	48
8	$CuBr_2$ (10)	TBHP (2.0)	30	2	34
9	-	TBHP (2.0)	30	2	0
10	$FeCl_2$ (10)	TBHP (2.0)	30	2	0

[a] Reaction conditions: **1a** (0.5 mmol), $TMSN_3$ (2.0 eq), catalyst, oxidant, CH_3CN (2 mL), stirred at 30 °C under Ar. TMS = trimethylsilyl. [b] Isolated yields.

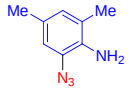
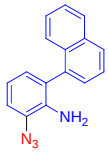
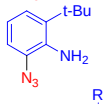
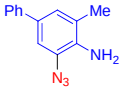
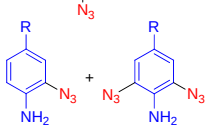
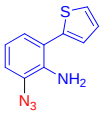
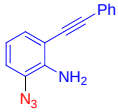
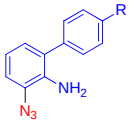
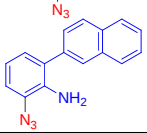
We commenced our study by investigating the C-H azidation of 2, 4-dimethyl aniline (**1a**). When the reaction was performed in the presence of azidotrimethylsilane ($TMSN_3$) and *tert*-butyl hydroperoxide (TBHP) using CuBr as the catalyst at 60 °C in CH_3CN, 2-azido-4,6-dimethylaniline (**2a**) was obtained in 28% yield (Table 1, entry 1). Taking into consideration that high temperature may lead to decomposition of the product, the reaction temperature was decreased from 60 °C to 30 °C, a slightly lower yield was obtained (Table 1, entry 2). To our delight, when the reaction time was decreased 12 h to 1 h, the yield was promoted to 56% (Table 1, entry 3). The highest yield appeared when the reaction time was 2 h, in 68% (Table 1, entry 4). In further step of exploring, we tried to decrease the amount of oxidant or catalyst. However, both resulted in low efficiencies (Table 1, entries 5-6). When the catalyst was replaced by CuCl or $CuBr_2$, the desired product **2a** was obtained only in 48% and 34% yield, respectively (Table 1, entries 7-8). Notably, this reaction did not work when CuBr was removed or replaced by $FeCl_2$ (Table 1, entries 9-10).

Under the optimized reaction conditions, the scope of this copper-catalyzed C-H azidation reaction was demonstrated with a series of aniline derivatives (Table 2). 2-*Tert*-butyl aniline (**1b**) also performed well to give the desired product **2b** in 68% yield (Table 2, entry 2). Notably, when *ortho*- unsubstituted electron-deficient and

Table 2. Cu-catalyzed Azidation of Anilines (1).[a]



1 2 3

entry	product	yield (%)[b]	entry	product	yield (%)[b]
1	 **2a**	68	17	 **2q**	54
2	 **2b**	68	18	 **2r**	57
3	 R = H, **2c**:**3c** = 1.7:1	73	19	 **2s**	63
4	R = *t*Bu, **2d**:**3d** = 1:1.8	85	20	 **2t**	67
5	R = c-Hex, **2e**:**3e** = 1:1.4	75	21	 **2u**	57
6	R = OMe, **2f**:**3f** = 1:1.7	61	22	 **2v**	49[e]
7[c]	R = CO_2Me, **2g**:**3g** = 2:1	63[d]			
8	R = $COCH_3$, **2h**:**3h** = 5:1	54			
9	 R = H **2i**	68			
10	R = Me **2j**	53			
11	R = F **2k**	67			
12	R = Cl **2l**	64			
13	R = OMe **2m**	43			
14	R = CN **2n**	55			
15	 **2o**	52			
16	 **2p**	68			

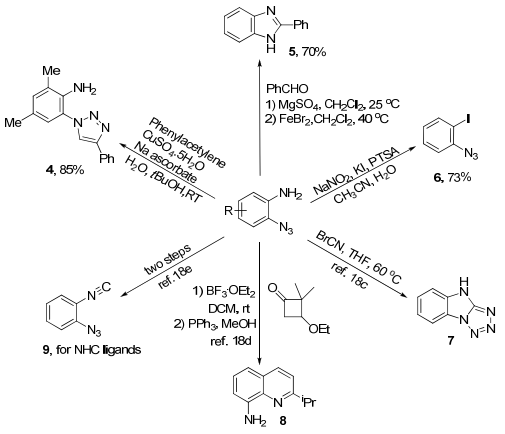
[a] Reaction conditions: **1** (0.5 mmol), $TMSN_3$ (1.0 mmol, 2.0 eq), CuBr (0.05 mmol, 10 mol %), TBHP (1.0 mmol, 2.0 eq), CH_3CN (2 mL), stirred at 30 °C under Ar. [b] Isolated yields. [c] Reaction carried out at 50 °C. [d] 25% of **1g** was recovered. [e] 36% of **1v** was recovered.

electron-rich anilines were employed as the substrates, both mono- and di-azidated products were obtained, which can be easily separated by column chromatography (Table 2, entries 3-8). One of the most readily available starting materials, aniline (**1c**), reacted smoothly in a total yield of 73% (the ratio of mono- to di-azidated product is 1.7:1). In the presence of an *ortho*-phenyl substituent, a series of substrates containing electron donating and withdrawing groups at the 2-phenyl ring of the anilines were tolerant in this transformation with moderate efficiencies (Table 2, entries 9-14). In addition, *ortho* 2-naphthyl (**1p**) and 1-naphthyl (**1q**) substituted anilines performed well in this transformation (Table 2, entries 16-17). 2-Chloro substituted aniline **1s** afforded the corresponding chloro-substituted products **2s** in 63% yield (Table 2, entry 19). Heterocycle-containing substrate such as 2-(thiophen-2-yl) aniline (**1t**) produced the desired **2t** in 67% yield (Table 2, entry 20). Moreover, 2-(phenylethynyl) aniline (**1u**) containing an alkynyl group also reacted smoothly with moderate yield (Table 2, entry 21).

It's noteworthy that when secondary amine was employed, this amino group directed *ortho* azidation reaction also underwent well. However, the biggest obstacle

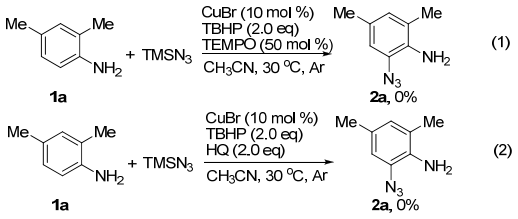
for secondary amine is that a large amount of starting material remained, thus leading to relatively low yields. Elevating the reaction time or increasing the reaction temperature didn't significantly promote the conversion of the starting materials. Under the standard conditions, diphenyl amine (**1v**) yielded the desired product **2v** in 49% isolated yield with 36% of **1v** recovery (Table 2, entry 22). The reaction of arylamines with a tertiary amino group did not work under the standard conditions (See Eq. S1-S2, SI). These results indicate that a free N-H bond is required for this transformation.

Scheme 2. Transformations of 2-Azidoaniline.

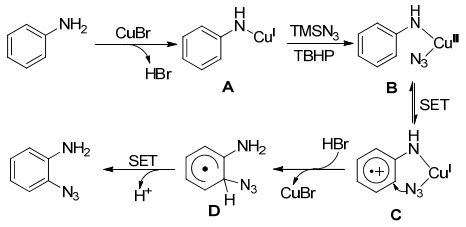


As mentioned above, aryl azides are versatile intermediates and building blocks in organic synthesis.[17,18] After this amino group directed *ortho* azidation protocol was established, we were looking forward to applying aryl azide in other transformations (Scheme 2). For the classical click reaction, 2-azido-4, 6-dimethylaniline (**2a**) was treated with phenylacetylene in the presence of catalytic amount of $CuSO_4$, thus affording the corresponding triazole **4** in 85% yield. When 2-azidoaniline (**2c**) was treated with benzaldehyde, benzimidazole **5** was produced in 70% yield.[18a] One of the advantages involving primary amino group as directing group is its possibility to be removed or go through other transformations. Referring to the well-known Sandmeyer Reaction, diazotization of **2c** with $NaNO_2$ followed by treatment with KI produced 1-azido-2-iodobenzene **6** in 73%.[18b] The azide group was well tolerated in this reaction, the resulting product could be subsequently used in further conversions. Moreover, 2-azidoanilines could also go through some other transformations according to literatures. 9*H*-Benzo[4,5]imidazo[1,2-*d*]tetrazole **7** could be easily prepared by the reaction of **2c** with BrCN *via N*-aryl cyanamide as the intermediate.[18c] Biologically important compound 8-amino quinoline **8** was constructed using 2-azido-aniline **2** as the starting material.[18d] In addition, 1-azido-2-isocyanobenzene **9** which is a precursor of *N*-heterocyclic carbene ligands, was synthesized from 2-azido-aniline **2**.[18e]

To further understand the mechanism, the reaction of **1a** in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) or hydroquinone (HQ) as the radical scavenger were tested, **2a** was completely inhibited in these reactions (Eq. 1-2), which demonstrates that a radical process may be involved in this process.



Scheme 3. Proposed Mechanism.



Although the mechanism of this transformation is not completely clear yet,[19] on the basis of above results, a possible mechanism is proposed in Scheme 3. Intermediate **A** is initially generated by the coordination of copper to the substrate.[20] Subsequently, intermediate **A** combines with an azide radical generated *in situ* from $TMSN_3$ and TBHP to form intermediate **B**. A single electron transfer (SET) from the aryl ring to the metal center (from **B** to **C**) is possibly involved in this process.[21] Then, azido group transfer into the aryl ring with release of CuBr forms intermediate **D**, which undergoes deprotonation *via* SET process leads to the product.

In conclusion, a novel and practical Cu-catalyzed *ortho*- C-H azidation of anilines has been developed. This azidation reaction is regiospecific at amino group's *ortho* position with broad substrate scope. This chemistry not only expands the scope of directing group, but also provides a novel C-H azidation approach leading to aryl azides which are of high synthetic value. Further studies to clearly understand the reaction mechanism and the synthetic applications are ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical data for products, NMR spectra of products. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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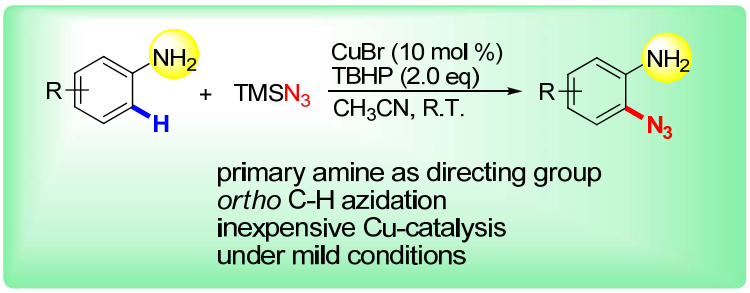
NH2
R
H
+ TMSN3
CuBr (10 mol %)
TBHP (2.0 eq)
CH3CN, R.T.
NH2
R
N3
primary amine as directing group
ortho C-H azidation
inexpensive Cu-catalysis
under mild conditions